The Influence of Cognitive Behavioral Therapy on Fatigue, Cognition and Inflammatory Biomarkers in Multiple Sclerosis Patients: Single Blinded Randomized Controlled Trial

Protocol

(Including Participant Flow Data Preparation & Data Results Elements)

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الباحثة :- شيماء طه ، انجي بدرالدين صلاح

القسم:- العلوم الاساسية

عنوان البحث: -

The efficacy of cognitive behavioural therapy on fatigue, cognition and inflammatory biomarkers in multiple sclerosis patients.

نحيطكم علما بموافقة لجنة أخلاقيات البحث العلمي علي خطة البحث المقدمة و تعتبر هذه الموافقة سارية اعتبارا من تاريخها.

و يرجي ملاحظة أنه يجب إخطار اللجنة علي الفور في حال وجود أي آثار سلبية غير متوقعة عليه قد تؤثر علي موافقة اللجنة.

رئيس لجنة أخلاقيات البحث العلمي

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كلية العلاج الطبيعي - جامعة القاهرة

The Influence of Cognitive Behavioral Therapy on Fatigue, Cognition and Inflammatory Biomarkers in Multiple Sclerosis Patients

Introduction:

There is a rising concern about quality of life of multiple sclerosis (MS) patients has emerged. Cognitive dysfunction with primary fatigue and there correlation to the level of disease inflammatory process has got great interest in MS research .

The aim of the present study was to examine the influence of using a computer-based cognitive behavioral therapy on primary fatigue, cognitive dysfunction, and inflammatory biomarkers for patients with MS.

Abstract :

A total of 40 MS patients (Expanded Disability Status Scale<5) were divided into two groups, both groups are suffering cognitive decline (using RehaCom software to assess attention/concentration, memory and reaction behavior) with primary fatigue according to the Fatigue Severity Scale (FSS>36). Patients with depression and sleep problems were excluded from the study. Patients in both groups have elevated serum levels of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ).

Patients in (G1) underwent conventional physical therapy program for MS including aerobic training, resistive training and a flexibility program, patients in (G2) underwent an intensive computer-based cognitive program for attention, concentration, memory and reaction behavior using the RehaCom software.

The conventional physical therapy interventions for both (G1) sustained for three months, 45 minutes to 1 hour, 3 times/week. The computer-based cognitive behavioral therapy for patients in (G2) was prescribed as following (45 minutes to 1 hour a session, 3 times/week for continues three months).

Results A statistically significant decrease in the level of primary fatigue (FSS scores) and in the serum levels of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) in (G2) patients compared to (G1) ($P < 0.001$), as well as a statistically significant higher scores for the cognitive capabilities (attention/concentration, memory & reaction behavior) in (G2) patients compared to (G1) ($P < 0.001$).

Conclusion The use of computer-based cognitive behavioral therapy in MS patients alone or as an adjunct to the conventional physical therapy program can help to relief symptoms of primary fatigue, improve cognitive capabilities. Computer -based cognitive behavioral therapy also has a great impact of reducing the level of inflammatory biomarkers in MS patients.

A. Subjects Selection:

Forty (40) MS patients (Expanded Disability Status Scale<5) were selected from Neurology Department Faculty of Medicine, Cairo University out-patient clinic , Multiple Sclerosis Research Unit, Cairo University and from Faculty of Physical Therapy ,Cairo University out-patient clinic. The patients were diagnosed and referred from a neurologist. All the patients were referred from a neurologist as a clinically definite MS according to Mcdonald criteria. The diagnosis was confirmed by MRI. The patients were assigned into two equal groups (Conventional physical therapy program)(G1) & (Computer-based cognitive behavioral therapy)(G2).

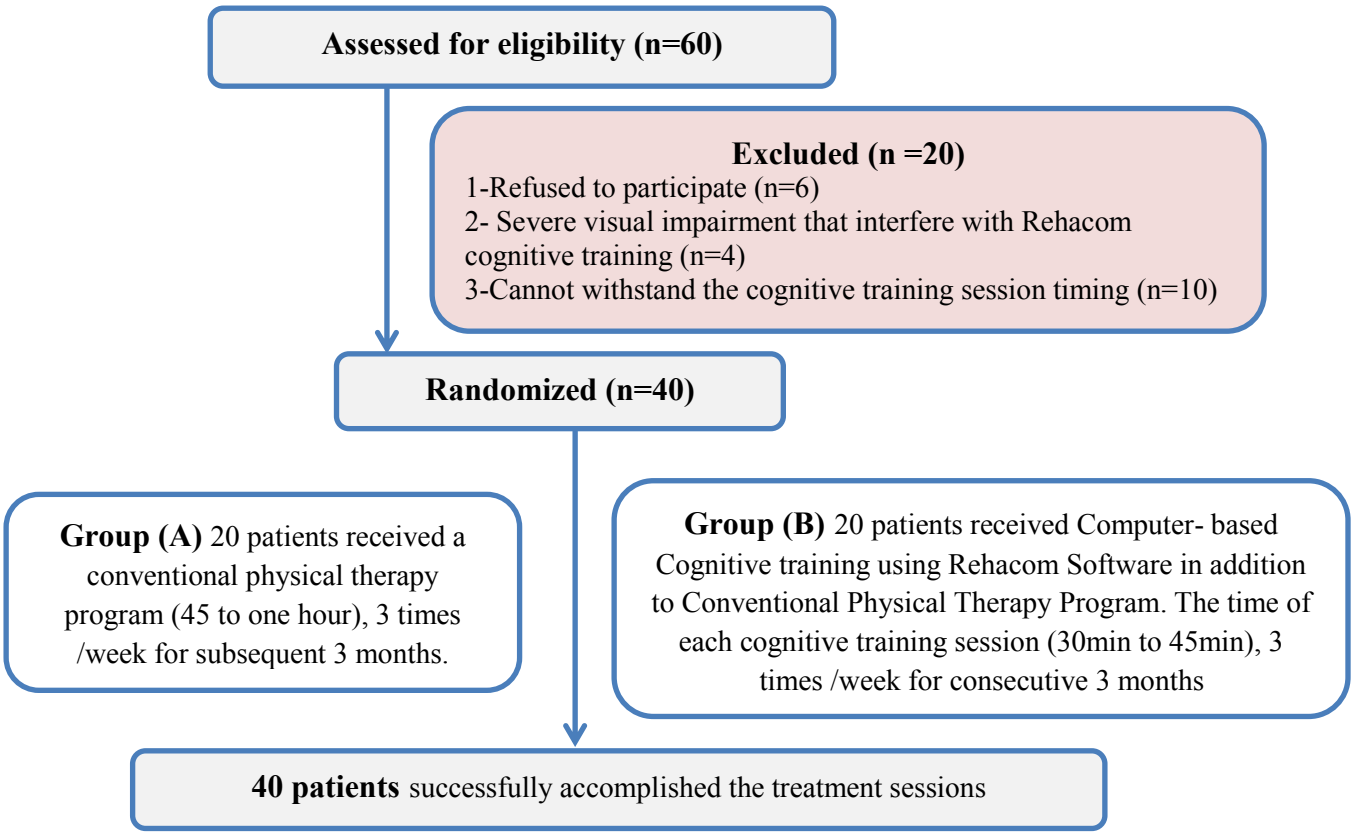
Design of the study

This single-blind, randomized controlled was performed in the cognitive training lab and in the outpatient physical therapy clinic, Faculty of physical therapy, Cairo University, during the period between December 2020 to May 2021. All procedures were in accordance with the Declaration of Helsinki and were approved by the Cairo university faculty of physical therapy Research Ethical Committee with registration number **(P.T.REC/012/003199).**

Subjects

Sixty Remitting-Relapse MS patients from both sexes their age ranged from 20 to 45 years, with (Expanded Disability Status Scale<5), who met all the inclusion criteria after signing an institutionally approved informed consent form prior to data collection .They were recruited from Outpatient Clinic, Faculty of Physical Therapy , Cairo University and the Outpatient Clinic of the MS unit at Neurology department, Faculty of Medicine, Cairo University in the period from December 2020 to May 2021 . The patients were diagnosed and referred by a neurologist. Diagnosis was confirmed according to Mcdonald criteria using Magnetic Resonance Imaging (MRI) Patients were excluded if they have severe visual, verbal or acoustic impairments that may interfere with cognition testing, serious chronic illness that could interfere with or modify assessment or treatment outcomes, low leukocyte count & elevated ESR as this interfere with cytokine levels, secondary causes of fatigue including severe depression (beck depression inventory (BDI ≥ 21) and sleep disturbance (Epworth sleepiness scale (ESS ≥ 12), inability to complete questionnaires as in severe cognitive impairment and illiteracy, if the Magnetic resonance imaging (MRI) of the brain showed plaques within the cingulate gyrus, insula , temporo-basal cortical areas or diffuse patchy frontal lesions as they usually complain from cognitive impairment independent of fatigue.

During initial assessment for eligibility 20 patients were excluded because six patients refused to participate in the study, 4 patients had some visual imparement, and 10 patients cannot withstand the cognitive training session. Forty patients received verbal and written explanation regarding the study purpose and procedures; if they agreed to participate they signed the consent form which was approved by the faculty of physical therapy. Then 40 Remitting-Relapse MS patients were allocated randomly by sealed envelope randomization into two groups: Both groups are suffering cognitive decline (using RehaCom software to assess attention/concentration, memory and reaction behavior) with primary fatigue according to the Fatigue Severity Scale (FSS>36). Patients with depression and sleep problems were excluded from the study. Patients in both groups have elevated serum levels of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ).



B. Instrumentations & Procedures :

A. Assessment Interventions:

• **Fatigue severity scale (FSS) :** It is valid and reliable scale used to assess fatigue severity in MS patients , and to distinguish fatigued MS patients from non fatigued MS patients(Armutlu et al,2007). It is self-reported questionnaire consisted of nine sentences. A list of statements/questions is provided. These statements are related to the different aspects of fatigue and how it affects the body.

Expanded Disability Status Scale (EDSS): was used to exclude patients with fatigue secondary to moderate to severe disability. It provides a total score on a scale that ranges from zero to ten. The first levels 1.0 to 4.5 indicate people with a

high degree of ambulatory ability. The subsequent levels 5.0 to 9.5 indicate loss of ambulatory ability. Grade (Zero) indicate normal neurologic exam. Grade (Five) indicate the ability of the patient to ambulate without aid or rest for 200 meter but disability is severe enough to impair full daily activities. (Ten) indicate death due to MS.

Beck depression inventory scale (BDI): was used to exclude patients suffering from fatigue secondary to depression. It composed of twenty one questions each with four possible responses ranging from "zero to three". Each question assess a specific symptom common among people with depression.

Epworth Sleepiness Scale (ESS): was used to exclude the patients suffering from fatigue secondary to sleep disturbance. It assess daytime sleepiness in people with multiple sclerosis . It consists of eight questions regarding sleep in different physiological and psychological conditions in multiple sclerosis patients.

Rehacom Software to assess cognitive function : It is a computer-based intensive cognitive rehabilitation test used to assess patient's cognitive functions. It includes 32 assessment tasks for attention, memory , logical reasoning& executive functioning. It composes of regular PC , 1G RAM , DVD drive, 100 GB hard drive with windows XP SP3, 128 MB RAM direct 3D graphic card , Screen at least 19" , regular PC keyboard or Rehacom panel & printer .The Rehacom software version is (patient enpult (1990-1997) EN/ISO-13485-certified). It is characterized by easy handling, close to reality , motivating for patients.

Blood analysis: A blood sample was collected from each patient in both groups before and after the 4 months treatment intervention. Assessment of patients on immunomodulatory therapy was postponed 36 hours from the last dose. Serum blood samples were immediately stored on ice. TNF-α and IFN- γ were measured using The Quantikine Human TNF-alpha & IFN-gamma Immunoassay ELISA kit . It is a 3.5 or 4.5 hour solid phase ELISA designed to measure human TNF-alpha & IFN-gamma in cell culture supernates, serum, and plasma. It contains E. coli-

derived recombinant human TNF-alpha, IFN-gamma and antibodies raised against this protein and antibodies raised against the recombinant factor. It has been shown to accurately quantities the recombinant factor (http://www.rndsystems.com/Products/DIF57&sta00c/aqQ).

B. Treatment Interventions:

Conventional Physical Therapy Program for patients in (G1):

Including (aerobic training 20 minutes, resistive training 15 minutes and flexibility program for 15 minutes), total conventional PT session timing (45 to one hour), 3 times /week for subsequent 3 months.

Computer- based Cognitive training using Rehacom Software in addition to Conventional Physical Therapy Program in (G2) :

Cognitive training including the attention/concentration, memory and reaction behavior domains, The time of each cognitive training session (30min to 45min), 3 times /week for consecutive 3 months.

Each domain in the cognitive training tests consists of one hundred levels of difficulty. Each level has an average 22 subtests. The maximum period of the session was about (60 minutes) for each patient with five minutes rest in between each level.

In Rehacom cognitive training, each patient is trained according to his/her primary cognitive level, which is predetermined during the assessment stage of the study.

C. Basic assumption:

It was assumed that:

- The Sample of this study represented the whole MS population..

- The instructions given to all patients during assessment accurately & faithfully followed.
- Patients motivation & cooperation were the same for each of them.

D. Null Hypothesis:

- There is no effect of using Rehacom Computer-based cognitive training on fatigue, cognition and proinflammatory ctokins in MS patients.

E. Data Analysis and Statistical Design:

All analyses were performed on SPSS for Windows version 22 (IBM Corp., Armonk, NY, USA).

At the baseline assessment, the mean values among the two groups were compared by one-way ANOVA for independent samples for continuous data or chi squared for categorical data.

The effects of the treatment pre-intervention and immediately post intervention were examined using the two factor ANOVA with factors 'time' (baseline, immediately post treatment intervention) on FSS ,RehaCom Cognitive domains' scores (attention/concentration, memory & reaction behavior), and serum levels data of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ).

Data were expressed as mean ± standard deviation (SD), A p value less than 0.05 was considered statistically significant.

F. RESULTS DATA ELEMENT

A total of 40 Remitting-Relapse MS patients with (Expanded Disability Status Scale<5) were divided into two groups, both groups are suffering cognitive decline (using RehaCom software to assess attention/concentration, memory and reaction behavior) with primary fatigue according to the Fatigue Severity Scale (FSS>36). Patients with depression and sleep problems were excluded from the

study. Patients in both groups have elevated serum levels of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ).

The patients were assigned into two equal groups, Control group patients (GA) and Study group patients (GB) . Upper limb motor function was assessed using (FMA-UE) and hand grip dynamometer and Magstim Rapid2 system with a figure-of-eight coil was used to determine the level of cortical excitability (CAMT and IAMT) for both groups (GA and GB).

I. General chronological features of the patients in both groups:

Forty MS patients were recruited in this study with total mean and standard deviation of age (27.3 ±3.982) years and total mean and standard duration of duration of illness (4.4± 1.128) years. The mean values and standard deviation of age in (GA) were (27.45 ±3.649) years and in (GB) were (27.15±4.380) years respectively. Also, the mean values of duration of illness in (GA) were (4.35±1.268) years and in (GB) were (4.45±0.999) years respectively (fig.). Comparison of the mean values of age and duration of illness in (GA) and the corresponding variables in (GB) revealed no significant differences where the P-values in both groups were ($P \geq 0.05$) .This means that the patient's age and duration of illness in both groups (G1 and G2) were statistically matched (table).

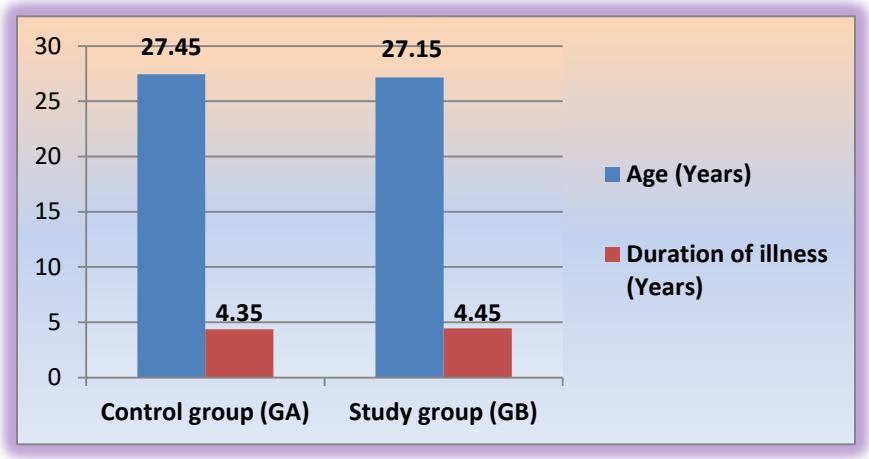


Fig ( ): Mean values of the Age and Duration of illness in both groups

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	p value	Mean Difference	Std. Error Difference	Upper	Lower
Age (Years)	Equal variances assumed	1.313	0.259	0.235	38	0.815	0.300	1.275	-2.281	2.881
	Equal variances not assumed			0.235	36.798	0.815	0.300	1.275	-2.283	2.883
Duration of illness (years)	Equal variances assumed	2.781	0.104	-0.277	38	0.783	-0.100	0.361	-0.831	0.631
	Equal variances not assumed			-0.277	36.022	0.783	-0.100	0.361	-0.832	0.632

* p values ≤ 0.05 was considered statistically significant

Table ( ): Mean values of the Age and Duration of illness in both groups

II. General characteristics of the patients in both groups

(Gender & Smoking history)

a. Gender difference between GA and GB:

The **number of male patients** in (GA) was thirteen with a percent of 46.4% nd in (GB) was fifteen with a percent of 53.6% of the total number within the male patients .While, The **number of female patients** in (GA) was seven with a percent of 58.3 % and in (GB) was five with a percent of 41.7% of the total number within the female patients (Fig.). There was no significant difference between both groups in the percentage of male and female as p-value of the Pearson Chi-Square was (0.490). This means that the patient's gender and distribution in both groups (GA and GB) were statistically matched (table 4).

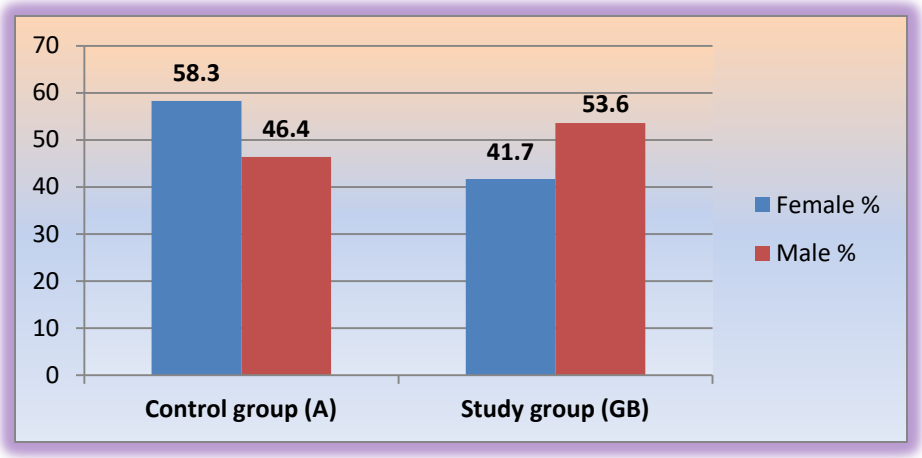


Fig ( ): Mean percentage of gender distribution in both groups

b. <u>Smoking history difference between GA and GB:</u>

The **number of Non-Smoking patients** in (GA) was ten with a percent of 43.5% and in (GB) was thirteen with a percent of 56.5% of the total number within the non-smoking patients .While, The **number of Smoking patients** in (GA) was ten with a percent of 58.8% and in (GB) was seven with a percent of 41.2%of the total number within the smoking patients (Fig.). There was no significant difference between both groups in the percentage of smoking history as p-value of the Pearson Chi-Square was (0.337). This means that the patient's smoking history and distribution in both groups (GA and GB) were statistically matched (table).

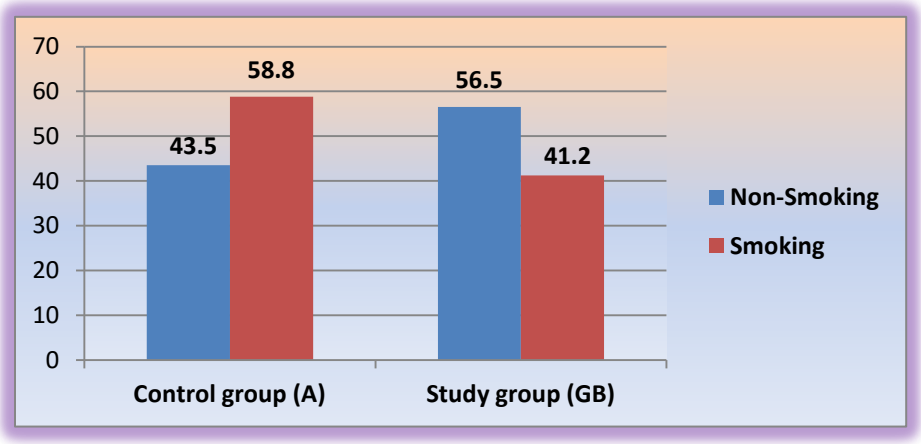


Fig ( ): Mean percentage of smoking history distribution in both groups

	Chi-Square Tests					
Main characteristics of patients		Value	df	p value	p value	p value
1. Gender difference	Pearson Chi-Square	.476(b)	1	0.490		
	Continuity Correction(a)	0.119	1	0.730		
	Likelihood Ratio	0.478	1	0.489		
	Fisher's Exact Test				0.731	0.366
	N of Valid Cases	40				
2. Smoking History		Value	df	p value	p value	p value
	Pearson Chi-Square	.921(b)	1	0.337		
	Continuity Correction(a)	0.409	1	0.522		
	Likelihood Ratio	0.925	1	0.336		
	Fisher's Exact Test				0.523	0.262
	N of Valid Cases	40				

* p values ≤ 0.05 was considered statistically significant

Table ( ): Percentage of Gender & smoking history distribution in both groups

III. The mean value of Expanded disability status scale (EDSS) scores in both groups:

The mean values of EDSS scores in (G1) and (G2) were (4.17±1.44), and (4.0±1.74) respectively. Comparison of the mean score of EDSS for both groups showed was no significant difference between both groups in the level of disability regarding the mean values of EDSS as p-value of the Pearson Chi-Square was (0.337). This means that the patient's EDSS in both groups (GA and GB) were

statistically matched Where the t and P-values were (2.98, 0.3368) (table ( ) and Fig ()).

Table (): Expanded disability status scale (EDSS) of primary fatigued (G1) and Non-fatigued MS patients (G2).

Patient groups	Expanded disability status scale scores (EDSS)		
	Mean ±SD	**t-value**	**P-value**
Control Group (G1)	4.17 ±1.72	**2.98**	**0.3368**
Study Group (G2)	4.0 ±1.34		

SD: standard deviation, Significant: P* < 0.05

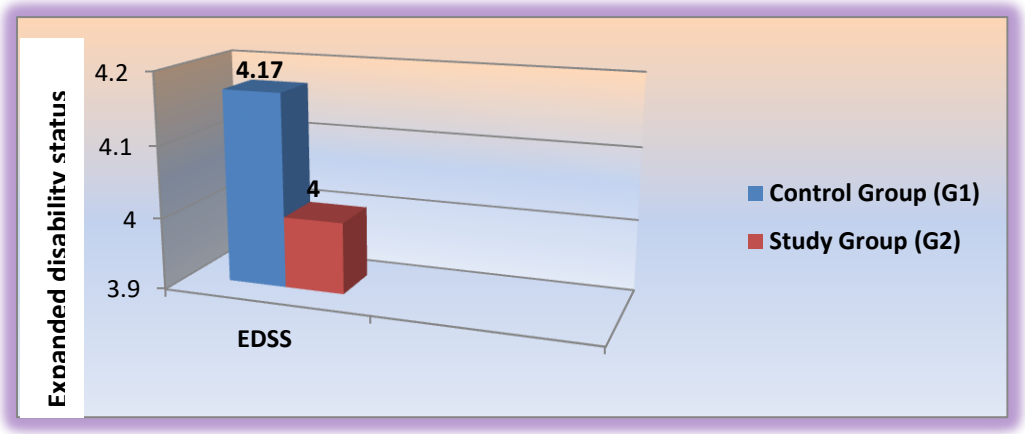


Fig.(): Mean value of the (EDSS)in both groups

IV- The Baseline Rehacom Cognitive Baseline results in (G1) and (G2):

T test was used to compare the mean value and standard deviation of the Baseline Rehacom cognition results between both groups (G1 and G2) .

a- The Baseline mean values of Attention/Concentration (AC) test of Rehacom in both groups

The mean values of total score of Baseline maximum reaction time in (G1) and (G2) were **(42138.7 ± 5756.2ms)** and **(41388.9 ± 5460.8ms)** respectively. Comparison of the mean values of Baseline maximum reaction time in both groups using T test , revealed no significant difference between both groups in Baseline mean values of Attention/Concentration (AC) test, where the t and P-values were (3.29, 0.415) (table ( ) and Fig ()).

(table 6,fig 26).

The mean values of total score of Baseline minimum reaction time in (G1)and (G2) were **(35273.4 ± 11257.4ms)**and **(32273.4 ± 11257.4ms)** respectively. Comparison of the mean values of Baseline minimum reaction time in both groups using T test , revealed no significant difference between both groups in Baseline mean values of Attention/Concentration (AC) test, where the t and P-values were (4.19, 0.365) (table ( ) and Fig ()).

b. <u>The Baseline mean values of Figural Memory (FM) test of Rehacom in both groups</u>

The mean values of baseline total score of the percentage of correct responses in (G1) and (G2) were **(58.2± 6.94%)** and **(60.3± 8.04)** respectively . Comparison of the mean values of Baseline percentage of correct responses in both groups using T test , revealed no significant difference between both groups in Baseline percentage of correct responses between both groups , where the t and P-values were (4.72, 0.246) (table ( ) and Fig ()).

The mean values of baseline total score of the solution time in (G1) and (G2) were **(2424.8 ± 584.9 ms)** and **(2606.9± 594.9)** respectively. Comparison of the mean values of Baseline total score of the solution time in both groups using T test , revealed no significant difference between both groups in Baseline solution time between both groups , where the t and P-values were (3.371, 0.278) (table ( ) and Fig ()).

c. <u>The Baseline mean values of Reaction behavior (RB) test of Rehacom in both groups</u>

The mean values of total Baseline score of the percentage of correct reactions in (G1) and (G2) were **(63.2± 6.14%)** and **(65.9± 6.82 %)** respectively .

Comparison of the mean values of Baseline total score of the percentage of correct reactions in both groups using T test , revealed no significant difference between both groups in Baseline percentage of correct reactions between both groups , where the t and P-values were (4.371, 0.318) (table ( ) and Fig ()).

The mean values of total score of the median reaction time in (G1) and (G2) were **(1664.8 ± 584.9 ms)** and **(1705.5 ± 601.2 ms)** respectively. Comparison of the mean values of Baseline total score of the median reaction time in both groups using T test , revealed no significant difference between both groups in Baseline median reaction time between both groups , where the t and P-values were (4.021, 0.288) (table ( ) and Fig ()).

Table (6): Baseline Mean values of the different variables of attention/concentration and reaction behavior tests for (G1) and (G2) in Rehacom cognition testing.

Variable		**Control group (G1)**	**Study group (G2)**	**T test**	
		Mean ±SD	**Mean ±SD**	**T value**	**P-value**
Attention & Concentration	Maximum reaction time **(ms)**	**42138.7 ±5756.2ms**	**41388.9 ±5460.8ms**	**3.29**	**0.415**
	Minimum reaction time	**35273.4±11257.4**	**32273.4 ±11257.4ms**	**4.19**	**0.365**

	(ms)				
Figural Memory	**% of correct responses**	**58.2± 6.94**	**60.3± 8.04**	**4.72**	**0.246**
	Solution Time (ms)	**2424.9± 584.9**	**2606.9± 594.9**	**3.371**	**0.278**
Reaction behavior	% of correct reactions	**63.2± 6.14**	**65.9± 6.82**	**4.371**	**0.318**
	Median reaction Time **(ms)**	**1664.8 ± 584.9 ms**	**1705.5 ± 601.2 ms**	**4.021**	**0.288**

SD: standard deviation,S:significant * : P ≤ 0.05 .

V- The Baseline mean values of laboratory Proinflammatory cytokines in (G1) and (G2):

T test was used to compare the mean value and standard deviation of the proinflammatory cytokines laboratory results (TNF-α and IFN-γ) between both groups (G1 and G2).

The Baseline mean values of the total results of Tumor necrosis factor alpha (TNF-α) in (G1) and (G2) were **(88.58± 15.94)** and **(89.52± 16.11)** respectively **.** Comparison of the mean values of Baseline total results of Tumor necrosis factor alpha (TNF-α) in both groups using T test , revealed no significant difference between both groups in Baseline median reaction time between both groups , where the t and P-values were (3.021, 0.381) (table ( ) and Fig ()).

The Baseline mean values of the total results of Interferon gamma (IFN-γ) in (G1) and (G2) were **(70.18± 10.71)** and **(68.65± 9.58)** respectively. Comparison of the mean values of Baseline total results of Interferon gamma (IFN-γ) in both groups using T test , revealed no significant difference between both groups in Baseline median reaction time between both groups , where the t and P-values were (3.018, 0.198) (table ( ) and Fig ()).

Table (7): Mean values of the TNF-α and IFN- γ for (G1) and (G2) in proinflammatory cytokines blood level.

Variable		**Control group (G1)**	**Study Group (G2)**	**F-value**	**P-value**
		Mean ±SD	**Mean ±SD**		
Level of proinflammatory cytokines	TNF-α **(pg/ml)**	**88.58± 15.94**	**89.52± 16.11**	**3.021**	**0.381**
		70.18±	**68.65±**	**3.018**	**0.198**

	IFN-γ **(pg/ml)**	**10.71**	**9.58**		

SD: standard deviation ,S:significant : P * ≤ 0.05 .

G. Definition of Terms

Attention/ Concentration:

It is the cognitive process that selectively concentrate on one aspect of the environment while ignoring other things (Bailey et al,2007).

Cognition:

It means knowing or perceiving. No matter what you are doing, your nervous system is always trying to provide you with the most complete and accurate picture of reality (Parkash et al, 2008) .

Cognitive dysfunction (CD):

It is losing the ability to create and refine surrounding environment, and making it impossible for you to use it (Jeffrey et al, 2007) .

Content validity:

It mean that the items of specific a measure represents all facets of a given social construct (Wilson et al,2012).

Concurrent validity:

It means that the test concurs with already existing standards contrast or variable. It provide evidence to defend the use of a specific test for predicting other outcomes. It is demonstrated when a test correlates well with a measure that has previously been validated (Sackett et al, 2007).

Contrust validity:

The degree to which a test measures internal inquires of a specific test. It is the degree that the measurement tools actually represent the construct being investigated (Kane, 2006).

Fatigue:

It is a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities (Krupp et al,2006).

Interferon-gamma (IFN-γ):

It is small class of glycoproteins capable of exerting antiviral activity in homologous cells through metabolic processes involving synthesis of RNA .It is formed by lymphocytes in response to mitogenic stimulation (Giovannoni et al ,2001).

Multiple Sclerosis(MS)

Is a chronic inflammatory demyelinating disease of the central nervous system (CNS) most commonly affecting young adults (Compston and Coles, 2008).

Primary fatigue (PF):

It is fatigue that result from centrally mediated processes characterized by the disease, such as demyelination and axonal loss in the central nervous system or immune actions . This result in a higher energy demand in certain brain areas with higher fatigue perception (Kos et al,2007) .

Pro-inflammatory cytokines:

These are Immuno- modulatory agents promote systemic inflammation including interferon gamma and tumor necrosis factor- alpha. Due to their proinflammatory action, they tend to make a disease worse by producing fever, inflammation and tissue destruction . Reducing the biological activities of proinflammatory cytokines can reduce the brunt of attack of diseases mediated by it (Heesen et al,2007).

Reaction behavior:

It is the human response to external stimulation (Marrie et al,2005).

Reaction time:

It is the elapsed time between the presentation of a sensory stimulus and the subsequent behavioral response (Desousa et al ,2002).

Tumor necrosis factor alpha(TNF-α):

It is a member of a group of cytokines that stimulate the acute phase reaction. It is produced chiefly by activated macrophages. It's primary role is in the regulation of immune cells (Prat & Martin ,2002).

Secondary fatigue (SF):

It is type of MS related fatigue not related directly to the disease pathological processes. It is result of accumulated burden of MS symptoms. It occur secondary to severe disability, reduced activity, psychological disorders as depression and sleep disturbances (Kos et al,2008).

H. References

Kujala P, Portin R, Ruutiainen J. The progress of cognitive decline in multiple sclerosis. A controlled 3-year follow-up. Brain. 1997;120(2):289–97.

Amato MP, Ponziani G, Siracusa G, Sorbi S. Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. Arch Neurol. 2001;58(10):1602–6.

Buchanan R, Radin D, Chakravorty BJ, Tyry T. Perceptions of informal care givers: health and support services provided to people with multiple sclerosis. Disabil Rehabil. 2010;32(6):500–10.

Brissart H, Daniel F, Morele E, Leroy M, Debouverie M, Defer GL. Remédiation cognitive dans la sclérose en plaques: revue de la littérature. Rev Neurol. 2011;167(4):280–90.

Benedict RH, Morrow SA, Guttman BW, Cookfair D, Schretlen DJ. Cognitive reserve moderates decline in information processing speed in multiple sclerosis patients. J Int Neuropsychol Soc. 2010;16(5):829–35.

Comi G. Effects of disease modifying treatments on cognitive dysfunction in multiple sclerosis. Neurol Sci. 2010;31(2):261–4.

Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 ;33(11):1444-.

Qassem T, Khater MS, Emara T, Rasheedy D, Tawfik HM, Mohammedin AS, et al. Normative data for healthy adult performance on the Egyptian–Arabic Addenbrooke's Cognitive Examination III. Middle East Curr. Psychiatry. 2015;22(1):27–36.

Shucard JL, Parrish JO, Shucard DW, McCABE DC, Benedict RH, Ambrus J Jr. Working memory and processing speed deficits in systemic lupus erythematosus as measured by the paced auditory serial addition test. J Int Neuropsychol Soc. 2004;10(1):35.

Reitan RM. Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills. 1958;8(3):271–6.

Elwan H, Saeed S, Fahmy I, Mahmoud A, El-kattan M, El-faioumy N. Cognitive dysfunction in multiple sclerosis. Egypt J Neurol Psychiatr Neurosurg. 2003;40:521–30.

Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science. 2005;308(5726):1314–8.

Ahmadi MA, Ashrafi F, Behnam B. Comparison of Montreal Cognitive Assessment test and Mini Mental State Examination in detecting cognitive impairment in relapsing-remitting multiple sclerosis patients. Int Clin Neurosci J. 2015;2(4):137–41.

El-Tamawy MS, Darwish MH, Ahmed SM, Abdelalim AM, Moustafa EB. Primary fatigue contributes to cognitive dysfunction in patients with multiple sclerosis. Egypt J Neurol Psychiatr Neurosurg. 2016;53(2):74.

Dineen RA, Vilisaar J, Hlinka J, Bradshaw CM, Morgan PS, Constantinescu CS, et al. Disconnection as a mechanism for cognitive dysfunction in multiple sclerosis. Brain. 2009;132(1):239–49.

Calabrese M, Agosta F, Rinaldi F, Mattisi I, Grossi P, Favaretto A, et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. Arch Neurol. 2009;66(9):1144–50.

M Tucker A, Stern Y. Cognitive reserve in aging. Curr Alzheimer Res. 2011;8(4):354–60.

Russo C, Morabito F, Luise F, Piromalli A, Battaglia L, Vinci A, et al. Hyperhomocysteinemia is associated with cognitive impairment in multiple sclerosis. J Neurol. 2008;255(1):64–9.

Amato MP, Zipoli V, Portaccio E. Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. J Neurol Sci. 2006;245(1-2):41–6.

Borghi M, Cavallo M, Carletto S, Ostacoli L, Zuffranieri M, Picci RL, et al. Presence and significant determinants of cognitive impairment in a large sample of patients with multiple sclerosis. PloS one. 2013;8(7):e69820.

Fischer JS, Priore RL, Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, et al. Neuropsychological effects of interferon β-1a in relapsing multiple sclerosis. Ann Neurol. 2000;48(6):885–92.